#### **TREATMENT OPTIONS**



#### **PRIMARY BILIARY CIRRHOSIS (PBC)**

Erik Christensen, Copenhagen

### Therapy for PBC - Difficulties

- Etiology is uncertain
- Therapies are based on ideas regarding pathogenesis
- Present medical therapies have a limited effect

• Advanced cases: Liver transplantation may be the only option

### Randomized clinical trials (RCTs) in PBC

- Relatively few
- Small in size

#### This means:

- Increased risk of imbalance between groups
- Results not very precise
- Increased risk of type 1 and 2 error
- Increased risk of publication bias

Pathogenetic features of Primary biliary cirrhosis (PBC)

- Destruction of small intrahepatic bile ducts
- "The florid duct lesion"
- Progressive cholestasis
- Cirrhosis
- Liver failure

# Medical therapies for primary biliary cirrhosis (PBC) tested in RCTs.

Therapy	Number of patients in RCT(s)	Effect	
Ursodeoxycholic acid (UDCA)	1422	((+))	
D-penicillamine	635	-	
Colchicine <sup>2</sup>	493	((+))	
Cyclosporin A	390	+	
Azathioprine	281	+	
Malotilate	101	(+)	
Methotrexate	99	-	
Prednisolone <sup>1</sup>	66	+	
Antioxidant supplementation	61	-	
Prednisone + Azathioprine <sup>1</sup>	50	+	
Budesonide <sup>1</sup>	39	+	
Chlorambucil	24	+	
Thalidomide	18	-	

#### PBC: Ursodeoxycholic acid (UDCA)

Cochrane Database Syst Rev. 2002;(1):CD000551

- Makes the bile "less toxic"
- UDCA (8-15 mg/kg/day) for 3 months to five years.
- 16 RCTs against placebo (n=15) or no intervention (n=1) in 1422 patients.
- UDCA significantly (P<0.05) reduced ascites, jaundice, serum bilirubin and liver enzymes.
- UDCA had no significant effects on mortality, liver transplantation, mortality or liver transplantation, pruritus, fatigue, s-albumin, prothrombin time, quality of life, liver histology, or portal pressure.

### Effect of UDCA on Pruritus and Fatigue

Heathcote J et al.UDCA (14 mg/kg/day) 111 pts.

Hepatology 1994;19:1149-56. Placebo 111 pts.



### PBC: The effect of UDCA on mortality

Cochrane Database Syst Rev. 2002;(1):CD000551

Study	UDCA n/N	Control n/N		Peto OR (95%Cl Fixed)	Weight %	Peto OR (95%Cl Fixed)
ATHENS	17/43	14/43		- 68	26.4	1.35[0.56,3.24]
BARCELONA	10/99	4/93			17.2	2.35[0.79,6.95]
DALLAS	3/77	3/74			- 7.6	0.96[0.19,4.89]
× FRANKFURT	0/10	0/10			0.0	Not Estimable
GÖTEBORG	1/60	1/56	<		<b>→</b> 2.6	0.93[0.06,15.12]
HELSINKI	0/30	2/31	<del>~ •</del>	22 14	2.6	0.14[0.01,2.21]
MAYO-I	4/89	7/91	35		13.7	0.57[0.17,1.94]
× MILAN	0/44	0/44			0.0	Not Estimable
X NEVVARK-II	0/9	0/10			0.0	Not Estimable
NEWCASTLE	1/22	3/24	←		4.9	0.38[0.05,2.86]
X TAIPEI	0/6	0/6			0.0	Not Estimable
X TOKYO	0/26	0/26			0.0	Not Estimable
TORONTO	5/111	9/111	385		17.4	0.54[0.19,1.60]
VILLEJUIF	3/73	3/73	100		- 7.6	1.00[0.20,5.10]
Total(95%Cl)	44 / 699	46 / 692			100.0	0.94[0.60,1.48]
Test for heterogeneity ch	ni-square=7.63 df=8 p=0.4	47				
Test for overall effect z	=-0.26 p=0.8					
			.1 .2	1	5 10 CAmore	

### PBC: Effect of UDCA on transplantation

#### Cochrane Database Syst Rev. 2002;(1):CD000551

#### Comparison: 01 Efficacy - UDCA versus placebo or no intervention **Outcome:** 02 Liver transplantation Weight Peto OR UDCA Control Peto OR Study n/N n/N (95%CI Fixed) % (95%Cl Fixed) ATHENS 4/43 3/43 1.36[0.29,6.32] 9.2 7/99 18.4 BARCELONA 7/93 0.94[0.32,2.77] 8/74 1.09[0.40,2.98] DALLAS 9/77 21.5 FRANKFURT. Not Estimable 0/10 0/10 0.0 GÖTEBORG 2/60 3/56 0.61[0.10,3.67] 6.8 3/31 0.13[0.01,1.31] HELSINKI 0/30 4.1 3/89 5/91 0.61[0.15,2.50] MAYO-I 10.9 0/44 MILAN. 0/440.0 Not Estimable 0/9 0/10 NEWARK-II. 0.0 Not Estimable NEWCASTLE 2122 1/24 4.0 2.20[0.22,22.37] 0/6 TAIPEL 0/6 0.0 Not Estimable 0/26 Not Estimable TOKYO 0/26 0.0 7/111 10/111 0.68[0.25,1.83] TORONTO. 22.3 1.00[0.06,16.14] VILLEJUIF 1/73 1/73 2.8 41/692 100.0 Total(95%Cl) 35/699 0.83[0.52,1.32] Test for heterogeneity chi-square=4.35 df=8 p=0.82 Test for overall effect z=-0.79 p=0.4 2 5 10 .1 **UDCAbetter** UDCA worse

# PBC: Effect of UDCA on mortality or transplantation

#### Cochrane Database Syst Rev. 2002;(1):CD000551

Study	UDCA n/N	Control n/N		Peto OR (95%Cl Fixed)	Weight %	Peto OR (95%Cl Fixed)
ATHENS	21 / 43	17/43			15.5	1.45[0.62,3.38]
BARCELONA	17/99	11/93			17.3	1.53[0.69,3.41]
DALLAS	12/77	11/74			14.1	1.06[0.44,2.56]
× FRANKFURT	0/10	0/10			0.0	Not Estimable
GÖTEBORG	3/60	4/56	39		4.8	0.69[0.15,3.15]
HELSINKI	0/30	5/31	<b>~=</b>		3.4	0.12[0.02,0.75]
MANCHESTER	4/14	2/14			→ 3.5	2.27[0.38,13.34]
MAYO-I	7/89	12/91	0.0		12.3	0.57[0.22,1.47]
× MILAN	0/44	0/44			0.0	Not Estimable
X NEVVARK-II	0/9	0/10			0.0	Not Estimable
NEWCASTLE	3/22	4/24	20		4.4	0.79[0.16,3.91]
X TAIPEI	0/6	0/6			0.0	Not Estimable
X TOKYO	0/26	0/26			0.0	Not Estimable
TORONTO	12/111	19/111	-		19.3	0.59[0.28,1.26]
VILLEJUIF	4/73	4/73	20		5.5	1.00[0.24,4.14]
Total(95%Cl)	83/713	89/706			100.0	0.90[0.65,1.26]
Test for heterogeneity chi	-square=10.99 df=9 p=0	).28				
Test for overall effect z=	-0.59 p=0.6					
NG.			.1 .2 UDCAbette	r UDC/	5 10 Aworse	

RCT with the largest effect of UDCA•Poupon R et al.N Engl J Med 1994;330:1342-7.•Placebo: 72 pts.UDCA (13-15 mg/kg/day): 73 pts.



The excess endpoints in the placebo group occurs after "crossover", i.e. **during** UDCA therapy.

The excess endpoints are transplantations, not deaths.

#### "Cross-over" from Placebo to UDCA after 2 years

Poupon R et al.

Gastroenterology 1997;113:884-90.



The excess endpoints in the Placebo group occurs *during* UDCA treatment

### PBC: The effect of UDCA on mortality including "cross-over" data Cochrane Database Syst Rev. 2002;(1):CD000551

#### Comparison: 04 UDCA-UDCA versus placebo/no intervention-UDCA Outcome: 01 Mortality

Study	UDCA n/N	Control n/N	Peto OR (95%Cl Fixed)	Weight %	Peto OR (95%Cl Fixed)
01 Jadad score = 4 or 5					
BARCELONA	10/99	4/93		11.2	2.35[0.79,6.95]
× FRANKFURT	0/10	0/10		0.0	Not Estimable
GÖTEBORG	1/60	1/56	<	→ 1.7	0.93[0.06,15.12]
HELSINKI	0/30	2/31	<	1.7	0.14[0.01,2.21]
MAYO-I	6/89	8/91		11.1	0.75[0.25,2.23]
× MILAN	0/44	0/44		0.0	Not Estimable
TORONTO	20/111	17/111		26.6	1.21[0.60,2.45]
Subtotal(95%Cl)	37 / 443	32/436		52.3	1.17[0.71,1.93]
Test for heterogeneity chi-sq	uare=4.54 df=4 p=0.3	34	6.0000 D 2000 C 2000		
Test for overall effect_z=0.6	0 p=0.5				
02 Jadad score = 1, 2 or 3					
ATHENS	17/43	14/43		17.2	1.35[0.56,3.24]
DALLAS	11/77	9/74		15.0	1.20[0.47,3.07]
X NEVVARK-II	0/9	0/10	1. Mar. 1. 2. Mar.	0.0	Not Estimable
NEWCASTLE	1/22	3/24	<	3.2	0.38[0.05,2.86]
× TAIPEI	0/6	0/6		0.0	Not Estimable
X TOKYO	0/26	0/26		0.0	Not Estimable
VILLEJUIF	6/73	10/73		12.3	0.57[0.20,1.61]
Subtotal(95%Cl)	35 / 256	36 / 256		47.7	0.96[0.57,1.62]
Test for heterogeneity chi-sq	uare=2.58 df=3 p=0.4	46			
Test for overall effect z=-0.1	6 p=0.9				
	70 / 600	69 / 602		100.0	4 0010 74 4 521
Test for beterogeneity objies	/2/033	10	the second	100.0	1.00[0.74,1.53]
Test for overall offect =-0.2	uare=7.40 ur=0 p=0.4	+3			
rest for overall effect z=0.3	2 p=0.7				
			.1 .2 1 UDAC better UD	5 10 ICAworse	

# PBC: Effect of UDCA on transplantation including "cross-over" data Cochrane Database Syst Rev. 2002;(1):CD000551

#### Comparison: 04 UDCA-UDCA versus placebo/no intervention-UDCA

Outcome:	02 Liver transplantation				
Study	UDCA n/N	Control n/N	Peto OR (95%Cl Fixed)	Weight %	Peto OR (95%Cl Fixed)
01 Jadad score :	= 4 or 5				
BARCELONA	7/99	7/93	· · · · · · · · · · · · · · · · · · ·	11.2	0.94[0.32,2.77]
× FRANKFURT	0/10	0/10	140	0.0	Not Estimable
GÖTEBORG	2/60	3/56	20 <u> </u>	4.2	0.61[0.10,3.67]
HELSINKI	0/30	3/31	<	2.5	0.13[0.01,1.31]
MAYO-I	7/89	7/91		11.2	1.02[0.35,3.04]
× MILAN	0/44	0/44	003	0.0	Not Estimable
TORONTO	15/111	22/111		26.7	0.64[0.31,1.29]
Subtotal(95%Cl)	31 / 443	42/436		55.8	0.70[0.43,1.14]
Test for heteroge	eneity chi-square=2.88 df=4 p=0.58				
Test for overall e	effect z=-1.42 p=0.16				
02 Jadad score :	= 1, 2 or 3				
ATHENS	4/43	3/43		- 5.6	1.36[0.29,6.32]
DALLAS	16/77	20/74		23.8	0.71[0.34,1.50]
X NEWARK-II	0/9	0/10	107.426	0.0	Not Estimable
NEWCASTLE	2/22	1/24		→ 2.5	2.20[0.22,22.37]
× TAIPEI	0/6	0/6	2016	0.0	Not Estimable
X TOKYO	0/26	0/26		0.0	Not Estimable
VILLEJUIF	4/73	12/73		12.4	0.33[0.12,0.92]
Subtotal(95%Cl)	26 / 256	36/256		44.2	0.66[0.38,1.14]
Test for heteroge	eneity chi-square=3.68 df=3 p=0.3				
Test for overall e	effect z=-1.48 p=0.14				
Total(95%Cl)	57 / 699	78/692		100.0	0.68[0.48,0.98]
lest for heteroge	eneity chi-square=6.59 df=8 p=0.58				
Test for overall e	effect z=-2.04 p=0.04		3		
			.1 .2 1 5 UDCAbetter UDCA	10 worse	

# PBC: Effect of UDCA on mortality or transplantation including "cross-over" data Cochrane Database Syst Rev. 2002;(1):CD000551

#### Comparison: 04 UDCA-UDCA versus placebo/no intervention-UDCA **Outcome:** 03 Mortality or liver transplantation UDCA Control Peto OR Weight Peto OR Study % n/N n/N (95%CI Fixed) (95%CI Fixed) 01 Jadad score = 4 or 5 BARCELONA 17/9911/93 11.7 1.53[0.69,3.41] FRANKFURT 0/10 0/10 0.0 Not Estimable GÖTEBORG 5/60 7/56 0.64[0.19,2.11] 5.3 HELSINKI 0/30 5/31 2.3 0.12[0.02.0.75] MAYO-I 13/8915/9111 5 0.87[0.39,1.94] MILAN 0/44 0/44 0.0 Not Estimable TORONTO 35/111 39/111 24.1 0.85[0.49,1.49] Subtotal(95%CI) 70/443 77/436 54.8 0.87[0.60,1.26] Test for heterogeneity chi-square=6.71 df=4 p=0.15 Test for overall effect z=-0.74 p=0.5 02 Jadad score = 1, 2 or 3 17/43 ATHENS 21/43 10.4 1.45[0.62,3.38] 27 / 77 29/74 17.2 DALLAS 0.84[0.43.1.62] MANCHESTER 4/14 2/14 2.4 2.27[0.38,13.34] NEWVARK-II 0/9 0/10 0.0 Not Estimable 0.79[0.16,3.91] NEWCASTLE 3/22 4/24 2.9 TAIPEI 0/6 0/6 0.0 Not Estimable TOKYO 0/26 0/26 0.0 Not Estimable VILLEJUIF 10/7322/73 12.2 0.39[0.18,0.84] Subtotal(95%CI) 65/270 74/270 45.2 0.81[0.54,1.22] Test for heterogeneity chi-square=6.61 df=4 p=0.16 Test for overall effect z=-1.02 p=0.3 Total(95%Ch 135/713 151 / 706 100.0 0.84[0.64,1.11] Test for heterogeneity chi-square=13.38 df=9 p=0.15 Test for overall effect z=-1.23 p=0.2 2 .1 5 10 UDCAbetter **UDCAworse**

# Long term UDCA therapy. Effect on mortality or liver transplantation (1)

Pares A et al. J Hepatol 2000; 32: 561-66.UDCA dose: 14-16 mg/kg/day

UDCA PLACEBO % years at risk UDCA PLACEBO 

## Long term UDCA therapy. Effect on mortality or liver transplantation (2)

Papatheodoridis G et al. Am J Gastroent 2002;97:2063-70
UDCA dose: 12 -15 mg/kg/day



# Long term UDCA therapy. Effect on mortality or liver transplantation (3)

#### •Combes B, et al. 70

#### Am J Gastroent 2004;99:269-



### **PBC: D-penicillamine vs. placebo**

Anti-inflammatory and copper-binding drug Tested versus placebo or no treatment in 635 patients Overall no consistent effect was found The incidence of side effects was high This drug is no longer used for PBC

#### PBC: Azathioprine 1-2 mg/kg/day

• Heathcote (Gastroenterology 1976;70:656-60) 22 patients AZA (2 mg/kg/day) 23 untreated controls

Multinational study (Gastroenterology 1985;89:1084-91)
 124 patients AZA (1 mg/kg/day)
 112 patients placebo

- AZA initially improved symptoms and biochemical tests.
- AZA improved survival slightly in the large study
- Side effects 10% more frequent during AZA.

#### **PBC:** Effect of Azathioprine

Gastroenterology 1993;105:1865-76

#### **Bilirubin:**



#### Albumin:



#### **PBC:** Glucocorticosteroids

A: Mitchison (J Hepatol 1992; 15;336-44) 36 patients **Prednisolone** (30-10 mg/day) vs. placebo for 3 years.

B: Leuschner (J Hepatol 1996;25:29-57) 30 patients: **Prednisolone** (10 mg/day) vs. placebo for 9 months. (All on UDCA)

C: Leuschner (Gastroenterology 1999;117:918-25) 39 patients: **Budesonide** k (9 mg/day) vs. placebo for 2 years. (All on UDCA)

Steroid had <u>significantly beneficial effect</u> on "<u>overall hepatic assessment</u>" (hepatic deaths, doubling of bilirubin, >6 g/l reduction in albumin, new symptoms of portal hypertension and occurrence of cirrhosis) (prednisolone 21% placebo 65%) (A), <u>biochemistry and histology</u> (B and C). No adverse effect was found on bone mineral content.

### **PBC: Prednisone + Azathioprine**

Wolfhagen FH.

(J Hepatol 1998; 29:736-42)

50 patients treated for 1 year (all received UDCA). <u>Prednisone</u> (30-10 mg/day) plus <u>Azathioprine</u> (50 mg/day) vs. Placebo

Prednisone + azathioprine led to

- Less pruritus
- A greater fall in enzymes and IgM
- Less histological disease activity
- Less progression of the histological stage

# **PBC: Prednisone + Azathioprine**Wolfhagen FH(J Hepatol 1998; 29:736-42)Pred + Aza + UDCA: dotted lineUDCA alone: solid line



### PBC: Cyclosporin A (2.5-4 mg/kg/day) versus Placebo

Minuk:	12 patients	(Gastroenterology 1988;95:1356-63)
Wiesner:	29 patients	(N Engl J Med 1990;322:1419-24)
Lombard:	349 patients	(Gastroenterology 1993:104:519-26)

All 3 studies found <u>beneficial effects</u> on <u>liver enzymes and</u> <u>bilirubin</u>.

In the largest study Cyclosporin A significantly <u>improved</u> <u>survival and liver related mortality.</u>

Cyclosporin A significantly reduced kidney function in 9% and caused hypertension in 11%. Close monitoring is necessary.

#### PBC: Colchicine (1-1.2 mg/day) versus placebo

#### Without concomitant UDCA therapy

- 4 RCTs including 241 patients
- Beneficial effects on liver function
- Little effect on histology
- No effect on survival or need for liver transplantation

With concomitant UDCA therapy

5 RCTs including 252 patients

- Small beneficial biochemical effect
- Long-term: No slowing of disease progression

#### PBC: Colchicine vs. Placebo

Battezzati . Aliment Pharmacol Ther 2001;15:1427-34



#### PBC: Colchicine versus Placebo Cochrane Review

Gong Y, Gluud C. Cochrane Database Syst Rev. 2004;(2):CD004481. Eleven randomised clinical trials involving 716 patients.

No significant effect on number of

- deaths (colchicine versus control (RR 1.21, 95% CI 0.71 to 2.06)
- deaths and/or liver transplants (RR 1.00, 95% CI 0.67 to 1.49)
- liver complications
- liver biochemical variables

#### PBC: Methotrexate (7.5-15 mg/week) vs. placebo

A: Hendrickse 60 pts. 6 years (Gastroenterology. 1999;117:400-7)
B: Gonzalez-Koch 25 pts. (All on UDCA) (J Hepatol. 1997;27:143-9)
C: Van Steenbergen 14 pts. (All on UDCA) (Acta Clin Belg 1996;51:8-18)

#### **Results:**

- A: Some effect on liver enzymes and immunoglobulins
  - No effect on mortality or liver transplantation
- B: No effect on biochemistry or histology
- C: No clinical or histological effect

PBC: Malotilate (1.5 g/day) versus placebo Multicentre RCT: 101 pt. Mean follow-up: 28 months (J Hepatol 1993;17:227-35)

**Results:** 

Significant beneficial effects on <u>liver enzymes</u>, <u>IgG</u> and <u>IgM</u>, <u>liver necrosis</u> and <u>inflammatory cell infiltration</u>

No effect on fibrosis, pruritus, disease progression or survival.

The observed benefits appeared too slight to recommend the drug as a single therapy. PBC: Thalidomide (100 mg/day) versus placeboMcCormick(J Hepatol 1994;21:496-9)Double-blind trial: 18 patients

#### **Results:**

- A possible effect on pruritus
- No other effects were found
- Side effects in 40%.

#### PBC: Antioxidants versus placebo

Prince (Aliment Pharmacol Ther 2003;17:137-41) Double-blind cross-over trial: 61 patientsPatients received either antioxidants (vitamins A, C, E, selenium, methionine and ubiquinone) or placebo for 3 months. Washout period 1 month.

**Results:** 

- No effect on fatigue or other symptoms
- No effect on liver tests

# Medical therapies for primary biliary cirrhosis (PBC) tested in RCTs.

Therapy	Number of patients in RCT(s)	Effect
Cyclosporin A	390	+
Azathioprine	281	+
Prednisolone <sup>1</sup>	66	+
Prednisone + Azathioprine <sup>1</sup>	50	+
Budesonide <sup>1</sup>	39	+
Chlorambucil	24	+
Malotilate	101	(+)
Ursodeoxycholic acid (UDCA)	1422	((+))
Colchicine <sup>2</sup>	493	((+))
D-penicillamine	635	-
Methotrexate	99	-
Thalidomide	18	-
Antioxidants	61	-

#### Therapies for <u>pruritus</u> in primary biliary cirrhosis (PBC) tested in RCTs.

Therapy	Number of patients in RCT(s)	Effect
Rifampicin	23	++
Rifampicin (versus Phenobarbitone)	22	+
<b>Diethylaminoethyldextran (DEAE-Dextran</b>	) 12	+
Naloxone	8	+
Flumecinol	50	(+)
DEAE-Dextran (versus Cholestyramine)	30	-

### Pruritus in PBC: Rifampicin (300-450 mg/day) versus placebo

Ghent

#### Gastroenterology 1988;94:488-93



#### Pruritus in PBC: Rifampicin (10 mg/kg) versus Phenobarbitone (3 mg/kg)

#### Bachs

#### Lancet 1989;1:574-6





#### Therapies for <u>osteopenia</u> in primary biliary cirrhosis (PBC) tested in RCTs.

Therapy	Number of patients in RCT(s)	Effect	
Transdermal Oestradiol	60	++	
Alendronate (versus Etidronate)	32	++	
<b>Etidronate (versus Sodium flouride</b>	e) 32	+	
Sodium flouride	22	+	
Etidronate	12	+	
Cyclosporin A	38	+	
Hydroxyapatite	36	+	
Vitamin K2	30	(+)	
Calcium gluconate	38	(+)	
Calcitonin	25	-	
Ursodeoxycholic acid (UDCA)	88	-	

 PBC Bone Loss: Transdermal Oestradiol 50 μg/day plus Medroxyprogesterone 2.5 mg/day versus No Hormone
 Omarsdóttir 18 patients J Intern Med 2004;256:63-9
 2 year RCT. All patients received alfacalcidol 0.25μg/day plus calcium 1 g/day



## PBC Bone Loss: Alendronate 10 mg/day versus Etidronate 400 mg/day (2/15 weeks) Guañabens 32 patients Am J Gastroenterol 2003;98:2068-74 2 year RCT. All patients received calcium and vitamin D supplementation

Change in lumbar bone mineral density

Alendronate: solid line

Etidronate: broken line



#### PBC Bone Loss: Etidronate (400 mg/day 2 of 11 weeks)

WolfhagenJ Hepatol 1997;26:325-301 year RCT.All patients received prednisone (~10 mg/day)



# Which medical therapies hold most potential in PBC?

General:

• Glucocorticosteroid plus azathioprine

For pruritus:

• Rifampicin

For bone disease:

- Alendronate
- Transdermal oestradiol

### Therapy of PBC – Conclusions 1

- Many different therapies have been tested in RCTs
- Highly effective treatments have not been identified
- For late stage disease: transplantation the only option
- Many RCTs are too small to allow a proper evaluation
- Larger multicentre RCTs are needed

### PBC therapy – Conclusions 2

- Despite significant effects on some biochemical variables, UDCA has no significantly beneficial effect on symptoms, mortality or the need for liver transplantation.
- More effective (immunosuppressive) therapies (including azathioprine and glucocorticosteroids) should not be withheld from the patients.
- However, even better therapies are needed.
- Better understanding of the etiology is important.
- Gene-technology may be a valuable tool.

#### ACKNOWLEDGEMENT

Thanks to the staff of the Cochrane Hepato-Biliary Group at the Copenhagen Trial Unit for help in identifying all the performed RCTs.

#### **PBC: Colchicine versus Methotrexate**

(Gastroenterology 1999;117:1173-80) Kaplan Colchicine (1.2 mg/day) 43 patients Methotrexate (15 mg/week) 42 patients All on UDCA 2 years follow-up Both led to decrease in pruritus and liver enzymes Only Methotrexate improved histology and IgG Neither drug had effect on bilirubin or albumin. Five patients receiving Methotrexate (and none on Colchicine) developed interstitial pneumonitis.